



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/DK84/00095 (22) International Filing Date: 27 September 1984 (27.09.84) (31) Priority Application Number: 4546/83 (32) Priority Date: 3 October 1983 (03.10.83) (33) Priority Country: DK (71)(72) Applicant and Inventor: GJERLØV, Mogens [DK/DK]; Saksenballe 9, Nr. Broby, DK-5672 Broby (DK). (74) Agent: LARSEN & BIRKEHOLM A/S SKANDINAVISK PATENTBUREAU ; Niels Hemmingsens Gade 32, DK-1153 Copenhagen K (DK). (81) Designated States: AT (European patent), AU, BE (European patent), BR, CH (European patent), DE (European patent), DK, FI, FR (European patent), GB (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent), US.</p>		<p>Published <i>With international search report.</i></p>
<p>(54) Title: PREPARATION FOR REHYDRATING MONOGASTRIC ANIMALS, INCLUDING HUMAN BEINGS, SUFFERING FROM DIARRHOEA AND USE THEREOF</p>		
<p>(57) Abstract</p> <p>A preparation for rehydrating monogastric animals, including human beings, and new-born ruminants suffering from diarrhoea which preparation is intended for being mixed in water comprises an absorbent intumescent agent, electrolytes and lactose-decomposing enzyme(s) and possible roughage, taste corrigents and/or dyestuffs. The intumescent agent constitutes 20-70% according to weight, preferably 40-43%, the electrolytes constitute 40-60% according to weight, preferably 53-57%, and the enzyme or enzymes constitute 0.01-5% according to weight, preferably 0.025-0.027%, and the balance is made up of roughage, taste corrigents and/or dyestuffs, where one type of roughage is wheat bran. It has proved particularly advantageous that the intumescent agent is vegetable fibres from the family Plantaginaceae and the enzyme is lactase with pH-optimum between 2 and 10, and the electrolytes are a mixture of two or more of the substances magnesium oxide, citric acid, potassium chloride, sodium citrate, sodium chloride, sodium bicarbonate, and glucose. An optimum effect is achieved when the fibres are dried crushed seed coats of <i>Plantago ovata</i>.</p>		

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Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GA	Gabon	MR	Mauritania
AU	Australia	GB	United Kingdom	MW	Malawi
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1 PREPARATION FOR REHYDRATING MONOGASTRIC ANIMALS,
INCLUDING HUMAN BEINGS, SUFFERING FROM DIARRHOEA
AND USE THEREOF

5 The invention relates to a preparation for rehydra-
ting monogastric animals, including human beings,
suffering from diarrhoea, especially non-infectious
diarrhoea and diarrhoea caused by rota and corona
viruses.

10

Even in well-organized agricultural countries with
good veterinary coverage, the mortality among new
-born animals such as calves and pigs is still very
great. For example, in Denmark in 1980 there were
15 destroyed about 180,000 calves, which corresponds to
nearly 20% of the calves born every year. The cause
of a number of the deaths among calves, and also of
a number of corresponding deaths among sucking pigs,
is that they become stressed when they are weaned and
20 placed, for example, in common sties or folds. When
the animals are removed and thus no longer receive
mother's milk, right up to half of the animals devel-
op diarrhoea because they become stressed due to
change of fodder, transportation etc. It is assumed
25 that half of the deaths are due to diarrhoea which
arises within the first month after their birth. A
number of the calves also suffer from rota and corona
virus infection, which is a contagious intestinal
infection where cows are virus carriers and infect
30 the calves. The disease is caused by ia. strongly
reduced production of lactase, so that the animals
cannot decompose the lastose in the milk with which
they are fed, and hereafter diarrhoea is quickly
developed by osmotic effect in the intestinal canal.



- 1 New-born calves and pigs with diarrhoea will lose considerably in weight because of dehydration and many die.
- 5 The object of the invention is to present a preparation for the treatment of diarrhoea, so that a very large number of the sick animals can be cured in very few days, whereby deaths due to loss of fluid is avoided and for the calves a higher growth is obtained.
- 10 ed.

This is achieved by composing the preparation as disclosed in the characterising part of claim 1. Surprisingly, it has been shown that a mixture of an

15 absorbent intumescent agent, lactose-decomposing enzymes and one or more electrolytes is a quick and effective agent against diarrhoea without any apparent side effects and with a better effect than with the individual components alone. The agent can be used

20 for the treatment of diarrhoea among all offspring of ruminants as long as these are one-stomached, ie. before they have begun cud-chewing, and for the treatment of non-infectious diarrhoea and diarrhoea caused by rota and corona viruses among all other one-stom-

25 ached animals, including human beings. The lactose-decomposing enzyme decomposes that lactose which, for example, a calf suffering from diarrhoea is itself unable to decompose and digest. Non-decomposed lactose in the intestinal canal contributes to worsening an

30 attack of diarrhoea. With certain other methods of treatment, it has been suggested that the lactose be decomposed in the milk before the calf receives the milk, but with the preparation according to the invention, the lactose is not decomposed until inside



- 1 the calf's stomach and intestine which results in fewer side effects, for example in the form of sitiophobia.
- 5 The agent is produced quite simply by weighing out and mixing the individual parts so that the finished agent is supplied as a dry powder ready for use.

Another great advantage of the preparation according to the invention is that it is possible to cure animals of diarrhoea without the use of normal antibiotics, and thus avoiding the disadvantages here- with in the form of medicinal residues in the animal, and the possibilities of developing bacteria strains resistant to antibiotics.

According to the invention it is very advantageous that the electrolytes in the preparation comprise such salts that replace salt lost by diarrhoea since by rehydration it is merely necessary to administer a preparation which will bring about both rehydration or stop dehydration and provide the lost salts and fluid.

- 25 When as disclosed in claim 3 the preparation comprises a buffer, it is not necessary to protect the enzymes by adopting special measures since the preparation itself for a period of up to 6 hours stabilises the pH-value of the stomach so that the enzymes are not inactivated, and it is not necessary to wait for the dissolution of a coating or the like in the intestine, the enzyme being immediately ready to perform its function. Thus protective measures for the enzyme are also spared.



1 The component parts must be such which are pharmaceu-
tically tolerable and a combination of the parts men-
tioned in claim 4 makes it possible to fulfill the
purpose of the present invention.

5

By composing the preparation as disclosed in claim 5
there is obtained a simple preparation which has the
required properties, ie. stopping diarrhoea, provid-
ing the necessary salts, providing lactase and bring-
10 ing it uninfluenced through the stomach in a simple
manner.

It is especially advantageous to compose the agent
as disclosed in claim 6, the reason being that it has
15 been shown that the absorbent vegetable fibres swell
up in the intestine in a very suitable and natural
manner, which gives the contents of the intestine a
gelatinous consistency so that the faeces will have
a normal consistency already a few hours after the
20 first feeding with the agent. The more quickly that a
diarrhoea from which a calf or sucking pig is suffer-
ing is brought under control, the greater are the
chances of the animal surviving. The glucose content
and the necessary salts in the correct amounts will
25 promote the absorption of nutrients and give the
weakened animal an easily transformable energy.

Practical applications and experiments have shown
that the agent according to the invention is par-
30 ticularly effective when the fibres are seed coats
as disclosed in claim 7.

The relation between the individual components in
the preparation according to the invention can vary



1 greatly, but it has been shown that the optimum
effect and protection of the enzymes is achieved if
the individual components are used in the ratios as
disclosed in more detail in claim 8. If this agent
5 is used immediately when an animal shows the symptoms
of diarrhoea, and it is a question of so-called
problem stock, then the agent according to the inven-
tion should be used in the event of the animal mere-
ly refusing to drink up, and a case of diarrhoea can
10 normally be stopped merely by treating the animal
a few times. It is thus possible to put an immediate
stop to the life-threatening loss of water and salts
(electrolytes) so that by far the majority of the
animals attacked will survive and be restored to
15 health quicker than if they are only treated with
electrolytes alone or the water palliative fibres
alone. This quicker restoration of the animals will
therefore bring about a better growth which has been
proved by clinical experiments.
20

By composing the preparation as disclosed in claim 9,
there is obtained a preparation which will stop
diarrhoea among animals and provide rehydration since
the preparation will only have to be mixed in water
25 or milk or a water/milk mixture whereupon an animal
will willingly drink it.

For human application the preparation is composed
without roughage and dyestuffs but with a corrigent
30 having the composition mentioned in claim 10, a
composition as disclosed in claim 11 being particular-
ly preferred since such a preparation is effective and
at the same time has a pleasant taste.



1 Since vegetable fibres as disclosed in claims 3 and
4 are expensive to use, it is possible to replace
the organic absorbent intumescent with a synthetic
intumescent in the carboxymethyl cellulose in dif-
5 ferent configurations with various radicals and
various metals can be used. Innumerable different
carboxymethyl celluloses are known and all of these
can be used, but with different effect, the reason
being that they are available with both different
10 viscosity and different rates of intumescence. The
use of a synthetic intumescent results in a cheaper
product, and generally with sufficient applicability.

The preparation according to the invention as dis-
15 closed in claim 12 is used by pouring 40-55 g of the
mixture into lukewarm water, milk or a water/milk
mixture at around 38°C. The result is a mixture which
the animals are very willing to drink and which
quickly cures them of diarrhoea because the gel form-
20 ed by the agent in the intestinal canal has the fol-
lowing characteristics:

- 25 a) a protective effect on the actual intest-
inal mucosa,
- b) binds some of the bacteria and their
toxins to itself,
- 30 c) ensures a normal intestinal passage
(peristalsis),
- d) quickly stops the loss of fluid and
electrolytes,



1 e) buffers the capacity due to the added
electrolytes in the gel formed, protects
the added lactase from inactivation for
up to 6 hours, and

5 f) the lactase decomposes the lactose in the
intestine and thus recreates a normal
osmotic balance.

10 For human application the same results as mentioned
above will be obtained. If desired, cold liquid can
be used for the preparation.

Practical experiment with the preparation according
15 to the invention.

480 sucking calves, all of them two to three weeks
old, were taken in for rearing experiments under
uniform optimum conditions with regard to hygiene,
20 climate and feeding, the object being to test the
effect of the preparation on dietetic-conditioned
diarrhoea among sucking calves.

By the first feeding after the calves taken in had
25 been placed in the cow-house at the research station,
all of the calves each received three litres of a
conventional electrolyte/water mixture, after which
this was gradually changed during the course of five
days to up to 7 litres of milk substitute. The calves
30 also had free access to hay and ordinary fodder
supplements.

During the course of fourteen days from the time they
were taken in, 86 of the calves, ie. 17.9%, contract-



- 1 ed stomach/intestinal disturbances. These animals
were immediately treated with the preparation accord-
ing to the invention and as disclosed in claim 12.
- 5 73 of the sick calves, ie. 84.9%, were completely
cured within a few days. The 13 calves which were
not cured immediately by the treatment were then
given supplementary treatment with antibiotics.
- 10 From this it will be seen that the diarrhoea which
is contracted early by many calves fattened on full
milk and by sucking pigs is often due to virus
infections and to transport stress, stress as a
result of feeding change and stress from changed
15 environment etc., and can therefore be cured with the
preparation according to the invention without the
use of antibiotics. Only 13 animals out of 86, ie.
approx. 15%, required supplementary antibiotic treat-
ment.

20

Course of treatment when using the preparation.

- The agent is mixed in water and is dosed in accord-
ance with the weight of the animal, the amounts used
25 being as stated in the following table:

<u>Weight of animal</u>		<u>Dose per feeding</u>		<u>No. of feeds per 24 hours</u>	
	approx. 20 kg	½ l	water + approx. 25g		4
30	- 30 kg	1 l	- + approx. 50g		4
	- 40 kg	1½ l	- + approx. 75g	3-4	
	- 50 kg	2 l	- + approx. 100g	3	
	- 60 kg	2½ l	- + approx. 125g	3	



- 1 After the first twenty-four hours, it can be an advantage to add 25-50 g curdled milk product, for example soured milk, yoghurt, junket or the like, per litre. From the third day, one can gradually
5 change over to the normal mixed fodder.

There are also cattle stock among which stomach/intestine disturbances are a recurrent problem. In such cases it can be an advantage to give for example
10 the calves the preparation according to the invention as soon as they just refuse to drink up the normal feed, for example consisting of full-cream milk or other milk mixtures or the like.

15 Comparative experiment

The curative properties against diarrhoea of the preparation according to the invention were compared by a controlled experiment with the properties of
20 Calmix neo at a Dutch calf fattening station.

For the experiments there were used in all 230 calves which were divided in 5 groups of 46 animals each. They were placed in wooden pens with floor grating
25 and being ventilated. One week old calves were used. The animals were weighed before the experiment, after 29 days and after 58 days. At the beginning there is given 1.5 l water and 75 g electrolytes as first feeding. The fodder consisted of a bag of Heftica per
30 calf followed by Hemeka start and fattening according to the usual schedule.

In case of diarrhoea either the preparation according to the invention or Calmix neo is given.



1 The experiment results are given in the table below.

	Average results Curative treatment	Conservative treatment (Calmix neo)	Preparation according to the invention
5			
	No. of calves	15	15
	Average weight at start	41.6 kg	38.3 kg
10	after 29 days	47.5 kg	45.3 kg
	58 days	74.4 kg	73.7 kg
	Average weight after 29 days	5.9 kg	7.0 kg
15	58 days	32.8 kg	35.4 kg
	Average weight after 29 days	5.9 kg	7.0 kg
	29-58 days	26.9 kg	28.4 kg
20			
	Average Weight/day after 29 days	203 g	241 g
	59 days	565 g	610 g

25 The curative properties of the preparation prove to be good. After 58 days the calves showed an average of 2.6 kg larger growth than the control group which was treated with Calmix neo. Moreover, the average weight per day among the animals which were treated

30 with the preparation according to the invention, increased in the second period more than the animals treated with Calmix neo. This shows that not only are the absorption and the digestive capacity of the intestine less influenced but they are at the same



- 1 time more quickly recreated. This result supports the fact that the pharmacokinetics of the preparation according to the invention builds on a protection of the intestinal wall against pathogenic attacks
- 5 coupled with a compensation for lack of lactase by means of acid resistant lactase whereby the secretion as well as the osmotic component are combatted.

Example 1

10

The preparation according to the invention can be composed, for example, as follows:

1000 g contains:

15	Magnesium oxide	5.75 g	
	Citric acid	13.50 g	
	Potassium chloride	24.00 g	
	Sodium citrate	26.50 g	electrolytes
	Sodium chloride	41.50 g	
20	Sodium bicarbonate	68.00 g	
	Glucose	350.00 g	
	Terra rubrum	2.50 g	dyestuff
25	Wheat bran	68.00 g	roughage
	Isphagola husk (dried seed coats of plantago ovata)	400.00 g	absorbent fibre
30	Lactase	0.25 g	enzyme
	Total	1000.00 g	



- 1 The individual ingredients, all of which are available as dry powders, are mixed mechanically and are thereafter immediately ready for use.
- 5 The agent according to the invention must not be administered in dry form, but must be suspended in water and administered as a solution or suspension. The intumescence occurs hereafter in the intestinal canal during a suitable period, whereby by absorption
- 10 of fluid said intumescence swells up and gives the contents of the intestine a suitable consistency, and binds and receives some of the bacteria and their toxins so that a diarrhoea is at once stopped.

15 Example 2

The preparation according to the invention can also have the following composition which is particularly preferred for human application:

20

1000 g contains:

	Magnesium oxide	6.17 g
	Citric acid	14.50 g
25	Potassium chloride	25.75 g
	Sodium citrate	28.45 g
	Sodium chloride	44.56 g
	Sodium bicarbonate	73.00 g
	Glucose	375.80 g
30	Isphagula husk, crushed	429.50 g
	Lactase	0.27 g
	Oil of peppermint	2.00 g



1 Example 3

A suspension or solution of the preparation prepared in example 1 is produced by mixing 50 g preparation to 1 liter of water. The pH-value in the fresh preparation is 8.56. By filtration to a pH-value of 5.73 there is used 40.5 meq hydrochloric acid which shows that there is a not inconsiderable Buffer effect in the preparation which will "neutralise" the hydrochloric acid in the stomach and consequently protect the lactase. -

The chemicals used in the examples are ordinary commercial chemicals and the lactase is preferably CHBS lactase 25.000 from Chr. Hansens Laboratorium, Copenhagen.



1 P A T E N T C L A I M S

1. Preparation for rehydrating monogastric animals, including human beings, suffering from diarrhoea, characterised in that it comprises an absorbent intumescent, electrolytes, lactose-decomposing enzyme(s) and perhaps roughage, taste corrigent(s) and/or dyestuff.
2. Preparation according to claim 1, characterised in that the electrolytes comprise such salts as will replace salts lost by diarrhoea.
3. Preparation according to claims 1 or 2, characterised in that the electrolytes are composed in such a manner that they give a buffer effect in the preparation in solution or suspension.
4. Preparation according to claim 1, 2 or 3, characterised in that the intumescent is selected among vegetable fibres from the family plantaginacea, seeds or vegetable matter from the family linum, pectin, hemicellulose, carboxymethyl cellulose, methyl cellulose, perhaps pregelatinised starch and albumine tannate, the electrolytes are a mixture of two or more of the substances magnesium oxide, magnesium carbonate hydroxide, magnesium hydroxide, magnesium silicate, calcium silicate, calcium carbonate, alkali metal chlorides such as sodium or potassium chloride, alkali metal hydrogen carbonates such as sodium or potassium hydrogen carbonate, aluminium phosphate, aluminium hydroxide, citric acid and alkali metal citrates such as sodium or potassium citrate, enzymes are a lactase with



- 1 pH-optimum between 2 and 10, the roughage is a fibre material such as bran, especially wheat bran, and the dyestuff is a pharmaceutically tolerable dyestuff.
- 5 5. Preparation according to claim 4, c h a r a c -
t e r i s e d i n that the electrolytes are a mix-
ture of magnesium oxide, sodium chloride, potassium
chloride, sodium hydrogen carbonate, citric acid,
sodium citrate and glucose, the enzyme is lactase
10 with a pH-optimum between 5 and 8, the roughage is
wheat bran, and the dyestuff is terra rubrum.
6. Preparation according to any one of claims 1-5,
c h a r a c t e r i s e d i n that the intumescent
15 is vegetable fibres from the family plantaginacea.
7. Preparation according to claim 6, c h a r a c -
t e r i s e d i n that the fibres are in the form
of dried, crushed seed coats of Plantago ovata.
20
8. Preparation according to any one of claims 1-7,
c h a r a c t e r i s e d i n that the intumescent
constitutes 20-70 percentage by weight, the electro-
lytes constitute 40-60 percentage by weight, the
25 enzyme or enzymes constitute 0.01-5 percentage by
weight and the balance is made up of roughage and
perhaps taste corrigent(s) and/or dyestuff(s).
9. Preparation according to claim 8, c h a r a c -
30 t e r i s e d i n that as an intumescent it con-
tains 40 percentage by weight Isphagula Husk, 52.925
percentage by weight electrolytes which are made up
of 0.575 percentage by weight magnesium oxide, 1.35
percentage by weight citric acid, 2.4 percentage by



- 1 weight potassium chloride, 2.65 percentage by weight
sodium citrate, 4.15 percentage by weight sodium
chloride. 6.8 percentage by weight sodium hydrogen
carbonate and 35 percentage by weight glucose cal-
5 culated on the finished preparation, 0.025 percentage
by weight lactase, 6.8 percentage by weight roughage
in the form of wheat bran and 0.25 percentage by
weight dyestuff in the form of terra rubrum.
- 10 10. Preparation according to any one of claims 1-7,
c h a r a c t e r i s e d i n that the intumescent
constitutes 20-70 percentage by weight, electrolytes
constitute 40-60 percentage by weight, the enzyme or
enzymes constitute 0.01-5 percentage by weight and
15 the balance taste corrigents.
11. Preparation according to claim 10, c h a r a c -
t e r i s e d i n that as an intumescent it contains
approx. 43 percentage by weight Isphagula Husk being
20 ground, approx. 57 percentage by weight electrolytes
which are made up of 0.617 percentage by weight
magnesium oxide, 1.45 percentage by weight citric acid,
2.575 percentage by weight potassium chloride, 2.845
percentage by weight sodium citrate, 4.456 percentage
25 by weight sodium chloride, 7.3 percentage by weight
sodium bicarbonate, 37.58 percentage by weight glucose
calculated on the finished preparation, 0.027 percent-
age by weight lactase and 0.2 percentage by weight
taste corrigent in the form of oil of peppermint.
- 30 12. Use of a preparation according to any one of
the claims 1-9 for treating diarrhoea among monogastric
animals, including human beings, or new-born ruminants
by which a dose, preferably 40-55 g, is mixed in a



17

- 1 portion of lukewarm water or milk or a water/milk mixture, preferably 1 litre and at about a temperature of 38°C, and administered orally.

5



INTERNATIONAL SEARCH REPORT

International Application No PCT/DK84/00095

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
A 61 K 35/78, 33/00, 37/54, 31/715		
II. FIELDS SEARCHED		
Minimum Documentation Searched *		
Classification System	Classification Symbols	
IPC 2,3,4	A 61 K 31/70, 31/715, 33/00, 33/06, 33/08, 33/10, 33/14, 35/78, 37/48, 37/54 .../...	
IPC 1	A 61 k 19/00, 27/06, 27/14	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched *		
SE, NO, DK, FI classes as above		
III. DOCUMENTS CONSIDERED TO BE RELEVANT 1*		
Category *	Citation of Document, 1* with Indication, where appropriate, of the relevant passages 1*	Relevant to Claim No. 1*
Y	DE, B2, 2 455 281 (SYNTEX (USA) INC) 5 June 1975 & NL, 7415477 BE, 822770 FR, 2252848 US, 3898328 GB, 1465308 AT, 338034 JP, 50088212	1-11
Y	DE, B2, 2 611979 (A MAYER) 29 September 1977 & AT, 353542	1-11
Y	DE, A1, 2 644 197 (ARIZONA FEEDS) 12 May 1977, see inter alia page 9 & BE, 847008 US, 4010262 NL, 7611037 US, 4120952 AU, 18286 CA, 1069048 GB, 1569300 .../...	1-11
<p>* Special categories of cited documents: 1*</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search 1	Date of Mailing of this International Search Report 1	
1984-12-11	1984-12-18	
International Searching Authority 1	Signature of Authorized Officer 1*	
Swedish Patent Office	Martin Hjalmdahl	

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

II

Fields searched (cont)

National cl. 30h:2/02, 2/03

US cl. 424:94,153,154,155,156,157,180,195

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹⁰

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 12, because ^{it s/} they relate to subject matter ^{is} not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy
(PCT Rule 39 (iv)).

2. ☐ Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out ^{is}, specifically:

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ¹¹

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No ¹⁸
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Y	FR, M, 2 996 (LABORATOIRES LELONG) Bulletin officiel de la Propriété industrielle /BSM/, no 3 1965	1-11
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Y	US, A, 4 164 568 (BEECHAM GROUP LIMITED) 14 August 1979, see inter alia the claims and column 2, lines 5-15 & NL, 7703128 BE, 852562 FR, 2345155 DE, 2712786 AU, 23619 CA, 1075157 GB, 1581826 AU, 510209	1-11
	... /...	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷	Relevant to Claim No ¹⁸
Y	WO, A, 82,02650 (N W VON MAGIUS) 19 August 1982, se inter alia the claims and page 5, lines 1 to 4 & EP, 0071623 AU, 80848	1-11
Y	Chemical Abstracts, Vol. 98 (1983), abstract No. 204 438 g, Jpn. Kokai Tokkyo Koho JP 58 39,625 (83 39,625)	1-11